Response

Claims 1-9 and 11 are currently pending in the present application.

The Applicants have amended claim 1 to highlight the non-obvious nature of the present invention. Claim 1 now includes the parameters of claim 3. Claim 3 has been cancelled.

Claim 1 now identifies the type of colloidal structures that are formed by the spontaneously dispersible pharmaceutical composition of the present invention. Support for the added claim language which refers to the colloidal structures may be found on page 2, lines 20, 22 and 23 of the specification. Such language highlights the intended use of the pharmaceutical compositions of the present invention and identifies that the present invention is not a colloidal suspension as claimed but produces colloidal structures when diluted in an aqueous environment. Thus, it is a type of colloid pre-concentrate.

The Examiner has rejected claims 1-9 and 11 under 35 U.S.C. § 103 (a) over Weder et al. (US 5726164) in view of Fricker et al. (US 5932243) and further in view of Goldstein et al. (US 5599808), Caravatti et al. (US 5093330) and/or Henry et al. (US 5736542). The Examiner states that Weder '164 teaches intravenous compositions comprising N-benzoyl-staurosporine, hydrophilic components, lipophilic components, and fatty acid triglycerides and surfactants. The Examiner states that the solubility problems of n-benzoylstaurosporine would have been overcome and apparent to one skilled in the art based on the combined teachings of Weder '164, Fricker '243, Goldstein '808, Caravatti '330 and/or Henry '542. The applicants respectfully disagree with the Examiner and request that the rejection under these grounds be withdrawn.

It is the Applicants' understanding that generally described properties of one active agent molecule cannot necessarily be applied to all other classes of active agent molecules. It is also the Applicants' understanding that a composition of one type can not be used across molecular classes to show that the composition could be used for a different class of molecules. There are different physical and chemical peculiarities of the compositions and the molecules for which they are used.

Weder '164 and Weder '898 teach forms of staurosporine derivatives which utilize nanosuspensions that are appropriate for intravenous injections (please see col 1, lines 40-42

and col 2, lines 48-53 of Weder '164 and col 1, lines 40 – 43 and col 2, lines 31-34 of Weder '898). Claim 1 of Weder '164 and Weder '898 require that water be a component of that invention. Thus they are nanosuspensions and are colloidal as claimed. This is an inherent requirement of those inventions which makes them suitable for intravenous use. The present invention is not limited to a specific amount of water or aqueous environment but becomes spontaneously dispersible in any general aqueous environment and this aspect of the invention allows solubility and good oral bioavailability to be conferred. The aqueous environment may be the stomach or a vessel outside of the body and therefore the compositions of the present invention may be dosed to patients either in diluted or undiluted form (to be diluted in the stomach environment).

Caravatti '330 teach triglycerides, paraffin hydrocarbons, polyethylene glycols, and higher alkanols to be used to create orally administered dry powders or capsules. Caravatti '330 also teaches fatty oils, paraffin oils or liquid polyethylene glycols to be used for soft gelatin capsule compositions. However, Caravatti '330 speak generically of these excipients and do not address the solubility or bioavailability problems which accompany patient dosing of N-benzoyl-staurosporine. Caravatii '330 do not claim any specific compositions which identify the need for colloidal pre-concentrates.

Goldstein '808 teach aqueous solutions of indolocarbazoles and in a minor way address the desire for an aqueous solution which is capable of solubilizing the comounds of that invention (please see col 1 lines 47 – 50 of Goldstein '808). However, Goldstein '808 do not identify the need for improved bioavailability nor do they teach colloidal or nano-suspensions. In fact, Goldstein '808 teach away from the usefulness of a colloidal solution, such as that which the present invention produces, for pharmaceutical or biological applications. In column 1, lines 43-48 Goldstein '808 state that "an indolocarbazole solution exhibiting incomplete solubilization (e.g. colloidal solution) in aqueous solution, or an indolocarbazole in dry form are each not useful for many pharmaceutical and biological applications." Therefore, the teachings of Goldstein '808 show that one skilled in the art would not be motivated to use colloids or colloid pre-cursors to achieve solubilization of N-benzoylstaurosporine for pharmaceutical purposes. The contrary teachings of Goldstein '808 actually represent strong evidence of nonobviousness (see In re Hedges, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685,687 (Fed. Cir. 1986)).

Nor do Goldstein' 808 teach or mention bioavailability problems or means to overcome them. Based on the teachings of Goldstein '808 one would not be motivated to use colloids or emulsions to overcome the problems in the manner in which the present invention does. One

must have some reasonable expectation that there is a chance of success in attempting a previously used approach to a combination of elements (see *In re Tomlinson*, 363 F.2d 928).

Henry ' 542 teach a formulation of N-benzoylstaurosporine which is dispersed, i.e. not-solubilized, in a single excipient, namely a saturated polyglycolysed glyceride (see col 1, lines 23-27 and also see Examples 1, 2, and 3 of Henry '542). While the invention of Henry '543 may be further dispersed in an aqueous medium (see col 2, lines 19 -20), there is no teaching of colloidal pre-concentrates which spontaneously become colloidal upon aqueous dilution, such as those of the present invention.

Fricker '243 teach microemulsion pre-concentrates for rapamycin. The rapamycin molecule claimed in Fricker '243 and the rapamycin class of molecules are large macrolide molecules exemplified by a cyclized linear hydrocarbon chain. N- benzoylstaurosporine is chemically similar to polyaromatic hydrocarbons. One cannot draw the same solubility inferences from rapamycin to N-benzoyl-staurosporine. There is no expectation of success for the use of a microemulsion of the type used in Fricker '243 with an active agent of the present invention. There must be a reasonable expectation of success suggested in the prior art (See *In re Dow Chem. Co.* 837 F.2d). One can not assume that rapamycin and N-benzoylstaurosporine have the same properties and thus the teachings of Fricker '243 would not lead one to make the present invention.

The applicants assert that one skilled in the art would not be motivated to use the elements of the present invention to make a pharmaceutical composition for N-benzoyl-staurosporine based on the teachings of Weder '164, Fricker '243, Goldstein '808, Caravatti '330 and/or Henry '542. None of these references teach a pharmaceutical composition for oral administration which is a colloidal pre-concentrate that is capable of solubilizing N-benzoylstaurosporine and which forms a colloidal suspension in a general aqueous environment in order to impart superb bioavailability. The Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 103 (a) on these grounds.

The Examiner has also indicated that the claimed limitations of bioavailability for the present invention would be determined by one skilled in the art without undue experimentation. The Applicants respectfully disagree with this characterization of the bioavailability parameters of the invention and request that the Examiner withdraw the rejection of claims on these grounds. The differences in bioavailability for the compositions of Fricker '243 and the present invention differ

markedly. For example, if one were to draw upon the biovailability shown in Fricker '243 they would see that, according to Example 4, the Cmax of the three compositions compared therein have a mean value that ranges between 7.83 ng/ml to 31.22 ng/ml of rapamycin (please refer to col 12 lines 35-42). In comparison, Example 5 of the present application shows that the Cmax values, in Table 2 on page 20, for the three compositions tested have a mean value that ranges from 757 to 853 nmol/L. It must be noted that some mathematical conversion is required for this comparison since the latter calculations are in nmol/L and not ng/ml as in Fricker '243. The following is a conversion to ng/ml for the data in Table 2 of the present invention:

Molecular weight of N-benzoylstaurosporine = 567 thus there are 567 ng/nmol

Mean value range of Table 2 in nmol/L = 757 – 853 – converted to ng/mL =

757 nmol/L * 567 ng/nmol * 1L/1000 mL = 429 ng/mL.

853 nmol/L * 567 ng/nmol * 1L/1000 mL = 484 ng/mL.

The comparison therefore of Fricker '243 Cmax versus the present invention is thus a range of 7.83 – 31.22 ng/mL versus 429 – 484 ng/mL. There is a difference in Cmax of between 14 to 55 times higher blood level due to amount of drug absorbed using the present invention versus that of Fricker '243 (i.e. 429/31.22 to 484/7.83). One could not make such a dramatic determination based on the molecules and composition of the present invention if they relied on the prior art teachings. The present invention is the product of significant testing and experimentation and it is tied to the peculiarities of the active molecules used therein.

Based on the foregoing, the Applicants do not believe that, as the Examiner states, Weder '164, Fricker '243, Goldstein '808, Caravatti '330 and Henry '542 show the relative skill in the relevant art which would lead one to create the present invention. The Applicants also assert that the combination of references would not motivate one skilled the art to make the present invention. The Applicants respectfully request that the Examiner withdraw his rejection under 35 U.S.C. § 103(a) under these grounds and that pending claims 1, 2, 4-9 and 11 be passed to allowance.

The Applicants believe that the Application is in condition for allowance and request early notice to that effect. If it will further prosecution of the application the Examiner is urged to telephone the Applicants' undersigned counsel at the number listed below.

Respectfully submitted,

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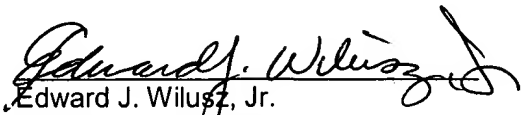

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